

APPENDIX A
CLEAN LISTING OF AMENDED CLAIMS

Listing of Claims:

1. **(Currently amended)** A water insoluble nanoparticle comprising at least one neutron capture element in an inorganic form.
2. **(Original)** A water insoluble nanoparticle comprising at least one neutron capture element in an inorganic form, said nanoparticle comprising a biocompatible outer layer.
3. **(Original)** A water insoluble nanoparticle as claimed in claim 2 wherein said outer layer is hydrophilic.
4. **(Original)** A nanoparticle as claimed in claim 1, 2 or 3 having a particle size of about 10^{-10} m to about 10^{-6} m.
5. **(Currently amended)** A nanoparticle as claimed in claim 1, 2 or 3 having a particle size of about 10^{-10} m to about 10^{-7} m.
6. **(Currently amended)** A nanoparticle as claimed in claim 1, 2 or 3 having a particle size of about 10^{-9} m to about 10^{-8} m.
7. **(Currently amended)** A nanoparticle as claimed in claim 1, 2 or 3 wherein said at least one neutron capture element is boron.

8. **(Currently amended)** A nanoparticle as claimed in claim 1, 2 or 3 wherein said at least one neutron capture element is selected from the group consisting of ^6Li , ^{22}Na , ^{22}Co , ^{113}Co , ^{126}I , ^{135}Xe , $^{148\text{m}}\text{Pm}$, ^{149}Sm , ^{151}Eu , ^{155}Gd , ^{157}Gd , ^{164}Dy , ^{184}Os , ^{199}Hg , ^{230}Pa , ^{235}U , and ^{241}Pu .
9. **(Currently amended)** A nanoparticle as claimed in claim 1, 2 or 3 wherein said neutron capture element is in its natural crystalline form.
10. **(Currently amended)** A nanoparticle as claimed in claim 1, 2 or 3 wherein said neutron capture element is in a particulate form.
11. **(Currently amended)** A nanoparticle as claimed in claim 1, 2 or 3 wherein said neutron capture element is in the form of a glass or a glass ceramic.
12. **(Currently amended)** A nanoparticle as claimed in claim 1, 2 or 3 wherein said neutron capture element is in the form of a polymerised inorganic matrix.
13. **(Currently amended)** A nanoparticle as claimed in claim 1, 2 or 3 wherein said neutron capture element is in the form of a sol-gel derived xerogel.
14. **(Currently amended)** A nanoparticle as claimed in claim 1, 2 or 3 wherein said neutron capture element is in the form of an organically modified ceramic and wherein the element comprises at least one bond to a hydrocarbon chain.
15. **(Currently amended)** A nanoparticle as claimed in claim 7 wherein said boron is in the form of:
- (i) $^{10}\text{B}_x\text{M}_n$;
 - (ii) $^{10}\text{B}_x\text{H}_n$; or
 - (iii) $\text{R}-^{10}\text{B}_n\text{-O}_n$

wherein M is a metal or is selected from the group consisting of nitrogen, carbon, oxygen, chlorine, bromine and fluorine, x and n are integers of 1 or above and R is a hydrocarbon chain or other organic chain.

16. **(Currently amended)** A nanoparticle as claimed in claim 7 wherein said neutron capture element is in the form of $(X-O-X)_n$ wherein n is an integer of 1 or above and X is the neutron capture element.

17. **(Canceled)**

18. **(Currently amended)** A nanoparticle as claimed in claim 2 or 3 wherein said biocompatible outer layer does not include intramolecular cross-linkages.

19. **(Currently amended)** A nanoparticle as claimed in claim 18 wherein said biocompatible outer layer is selected from the group consisting of polymers, organic or inorganic pharmaceutical excipients, low molecular weight oligomers, natural products, ionic surfactants and non-ionic surfactants.

20. **(Currently amended)** A nanoparticle as claimed in claim 18 wherein said biocompatible outer layer comprises an excipient selected from the group including gelatin, casein, lectine (phosphatides), gum acacia, calcium stearate, cholesterol, tragacanth, sorbitan esters, stearic acid, benzalkonium chloride, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, polyoxyethylene alkyl ether, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters polyethylene glycols, polyoxyethylene stearates, colloidal silicon dioxide, colloidal titanium dioxide, phosphates, sodium dodecylsulphate, carboxymethylcellulose calcium or sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, hydroxypropylcellulose, magnesium aluminium silicate, triethanolamine, polyvinyl alcohol (PVA), and polyvinylpyrrolidone (PVP).

21. **(Currently amended)** A nanoparticle as claimed in claim 18 wherein said biocompatible outer layer comprises a polymer selected from the group consisting of:

- (i) block copolymers;
- (ii) polyethylene glycol (PEG) or ethylene glycol copolymers;
- (iii) polysaccharides;
- (iv) poly (amino acids);
- (v) polyesters;
- (vi) alternating polymers;
- (vii) copolymers of styrene and maleic anhydride;
- (viii) polygalacturonic acid;
- (ix) copolymers of hydroxalkyl(meth)acrylate;
- (x) poly(α -L-glutamic acid) (PGA);
- (xi) biodegradable diamido-diamine polymers; and
- (xii) N-(2-hydroxypropyl) methacrylamide (HPMA) copolymers.

22. **(Currently amended)** A nanoparticle as claimed in claim 18 wherein said biocompatible outer layer comprises a surfactant selected from the group consisting of aerosol OT (dioctyl ester of sodium sulfosuccinic acid), polyoxyethylene sorbitan fatty acid ester, sodium lauryl sulfate, polyoxyethylene 20 sorbitan monolaurate, polyoxyethylene 20 sorbitan monopalmitate, polyoxyethylene 20 sorbitan monostearate, polyoxyethylene 20 sorbitan monooleate and lecithin N-(2-hydroxypropyl).

23. **(Currently amended)** A nanoparticle as claimed in claim 1, 2 or 3 wherein the neutron capture element is present as a layer or film around an inorganic nanoparticle core.

24. **(Currently amended)** A nanoparticle as claimed in claim 23 wherein said core is selected from the group consisting of mica, zeolites, TiO₂ spheres, ZrO₂ spheres or particles and organic polymer particles or spheres.

25. **(Currently amended)** A nanoparticle as claimed in claim 1, 2 or 3 wherein said nanoparticle further comprises a pharmacologically active substance.
26. **(Currently amended)** A nanoparticle as claimed in claim 25 wherein said pharmacologically active substance is loaded into said nanoparticle by absorption, adsorption or incorporation.
27. **(Currently amended)** A nanoparticle as claimed in claim 25 wherein said pharmacologically active substance is a chemotherapeutic agent.
28. **(Currently amended)** A nanoparticle as claimed in claim 1, 2 or 3 further comprising a further metal selected from the group consisting of vanadium (V), manganese (Mn), iron (Fe), ruthenium (Ru), technetium (Tc), chromium (Cr), platinum (Pt), cobalt (Co), nickel (Ni), copper (Cu), zinc (Zn), germanium (Ge), indium (In), tin (Sn), yttrium (Y), gold (Au), barium (Ba), tungsten (W), and gadolinium (Gd).
29. **(Original)** A nanoparticle as claimed in claim 28 wherein said further metal is present at a concentration of about 0.0001% wt/wt to about 0.1 % wt/wt.
30. **(Currently amended)** A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a water insoluble nanoparticle comprising at least one neutron capture element in an inorganic form.
31. **(Currently amended)** A pharmaceutical composition as claimed in claim 30 comprising a water insoluble nanoparticle according to claim 2 or 3.

32. **(Original)** The use of water insoluble nanoparticles comprising at least one neutron capture element in an inorganic form in the manufacture of a medicament for use in neutron capture therapy.

33. **(Currently amended)** A use as claimed in claim 32 wherein said neutron capture therapy is used for the treatment or ablation of cancer or other diseased tissues.

34. **(Original)** A use as claimed in claim 33 wherein said tumour is solid and discrete.

35. **(Original)** A use as claimed in any of claims 32 to 34 wherein said neutron capture therapy is administered over a period of one to fourteen days.

36. **(Currently amended)** A use as claimed in claim 32 wherein said nanoparticle is a nanoparticle according to claim 2 or 3.

37. **(Original)** A method for neutron capture therapy comprising:

- (i) administering a water insoluble nanoparticle having at least one neutron capture element in an inorganic form to an individual;
- (ii) allowing said nanoparticles to accumulate at a desired location in the body; and
- (iii) administering neutrons to said individual.

38. **(Currently amended)** A method as claimed in claim 37 wherein said neutron capture therapy is used for the treatment or ablation of cancer or other diseased tissues.

39. **(Original)** A method as claimed in claim 38 wherein said tumour is solid and discrete.

40. **(Currently amended)** A method as claimed in claim 38 or 39 further comprising a step of removing a tumour by surgery.

41. **(Currently amended)** A method as claimed in claim 38 or 39 further comprising a step of analysing the concentration of the neutron capture element at the desired location in the body.
42. **(Currently amended)** A method as claimed in claim 41 wherein said step of analysing comprises MRI, PET or SPECT imaging.
43. **(Original)** The use of water insoluble nanoparticles comprising at least one neutron capture element in an inorganic form in a method for neutron capture therapy.
44. **(Currently amended)** A use as claimed in claim 43 wherein said neutron capture therapy is used for the treatment or ablation of cancer or other diseased tissues.
45. **(Original)** A use as claimed in claim 44 wherein said tumour is solid and discrete.
46. **(Original)** A process for the preparation of water insoluble nanoparticles comprising at least one neutron capture element in an inorganic form, said process comprising:
- (i) providing at least a first mass of said neutron capture element in an inorganic form;
 - (ii) providing at least a second mass of the same type of material;
 - (iii) mixing said first and second masses in the absence of other abrasive material;
 - (iv) causing frictional abrasion between said first and second masses; and
 - (v) collecting said nanoparticles.
47. **(Original)** A process as claimed in claim 46 wherein at least one further, non abrasive material is included in said mixing step (iii).
48. **(Currently amended)** A process as claimed in claim 47 wherein said further, non abrasive material is selected from the group consisting of vanadium (V), manganese (Mn), iron (Fe), ruthenium (Ru), technetium (Tc), chromium (Cr), platinum (Pt), cobalt (Co), nickel (Ni),

copper (Cu), zinc (Zn), germanium (Ge), indium (In), tin (Sn), yttrium (Y), gold (Au), barium (Ba), tungsten (W), and gadolinium (Gd).

49. **(Currently amended)** A process as claimed in any of claims 46 to 48 wherein the resulting nanoparticles are characterised by the features of a nanoparticle according claim 2 or 3.

50-53. **(Canceled)**

54. **(New)** A nanoparticle as claimed in claim 7 wherein said boron is ^{10}B .

55. **(New)** A nanoparticle as claimed in claim 8 wherein said neutron capture element is in the form of $(\text{X-O-X})_n$ wherein n is an integer of 1 or above and X is the neutron capture element.

56. **(New)** A nanoparticle as claimed in claim 19 wherein said natural products are selected from the group consisting of gelatins, gums, fatty acids, soya bean oils and purified fractions thereof.

57. **(New)** A nanoparticle as claimed in claim 21 wherein said biocompatible outer layer comprises a block copolymer selected from the group consisting of poly(ethylene glycol-aspartate), block copolymers of ethylene oxide and propylene oxide, and tetrafunctional block copolymers derived from the addition of ethylene oxide and propylene oxide to ethylene diamine.

58. **(New)** A nanoparticle as claimed in claim 21 wherein said biocompatible outer layer comprises a polysaccharide selected from the group consisting of dextrin, dextran, chitosan (N-succinyl chitosan), carboxymethyl chitin, carboxymethyl pullulan and alginate.

59. **(New)** A nanoparticle as claimed in claim 21 wherein said biocompatible outer layer comprises a poly(amino acid) selected from the group consisting of poly [N-(2-hydroxyethyl)-L-

glutamine) (PHEG), β -poly(2-hydroxyethyl aspartamide) (PHEA), poly(glutamic acid), poly(aspartic acid), poly(lysine) and poly(L-lysine).

60. (New) A nanoparticle as claimed in claim 21 wherein said biocompatible outer layer comprises a polyester selected from the group consisting of poly(α -malic acid) and poly(β -malic acid).

61. (New) A nanoparticle as claimed in claim 21 wherein said biocompatible outer layer comprises the alternating polymer PEG-lysine.

62. (New) A nanoparticle as claimed in claim 21 wherein said biocompatible outer layer comprises a copolymer of hydroxalkyl(meth)acrylate selected from the group consisting of N-phenylpyrrolidone, poly(L-glutamic acid and hydroxyethyl-L-glutamine), poly(α -malic acid), polyaspartic acid-PEG copolymers, poly(L-lysine) and copolymers of polyethyleneimine.

63. (New) A use as claimed in claim 33 wherein said neutron capture therapy is used for the treatment or ablation of a cancer or diseased tissue selected from the group consisting of lymphomas, skin cancer, breast cancer, lung cancer, head and neck cancer, bone cancer, prostate cancer, cancer of the pancreas, cervical cancer, brain cancer, glioblastomas, primary and secondary metastases, benign and metastatic prostate cancers, and benign prostate hyperplasia.

64. (New) A method as claimed in claim 38 wherein said neutron capture therapy is used for the treatment or ablation of a cancer or diseased tissue selected from the group consisting of lymphomas, skin cancer, breast cancer, lung cancer, head and neck cancer, bone cancer, prostate cancer, cancer of the pancreas, cervical cancer, brain cancer, glioblastomas, primary and secondary metastases, benign and metastatic prostate cancers, and benign prostate hyperplasia.

65. (New) A use as claimed in claim 44 wherein said neutron capture therapy is used for the treatment or ablation of a cancer or diseased tissue selected from the group consisting of

lymphomas, skin cancer, breast cancer, lung cancer, head and neck cancer, bone cancer, prostate cancer, cancer of the pancreas, cervical cancer, brain cancer, glioblastomas, primary and secondary metastases, benign and metastatic prostate cancers, and benign prostate hyperplasia.

66. (New) A pharmaceutical composition as claimed in claim 30 comprising a water insoluble nanoparticle according to claim 6.

67. (New) A pharmaceutical composition as claimed in claim 30 comprising a water insoluble nanoparticle according to claim 7.

68. (New) A pharmaceutical composition as claimed in claim 30 comprising a water insoluble nanoparticle according to claim 15.

69. (New) A pharmaceutical composition as claimed in claim 30 comprising a water insoluble nanoparticle according to claim 16.

70. (New) A pharmaceutical composition as claimed in claim 30 comprising a water insoluble nanoparticle according to claim 23.

71. (New) A pharmaceutical composition as claimed in claim 30 comprising a water insoluble nanoparticle according to claim 29.

72. (New) A use as claimed in claim 32 wherein said nanoparticle is a nanoparticle according to claim 6.

73. (New) A use as claimed in claim 32 wherein said nanoparticle is a nanoparticle according to claim 7.

74. (New) A use as claimed in claim 32 wherein said nanoparticle is a nanoparticle according to claim 15.

75. (New) A use as claimed in claim 32 wherein said nanoparticle is a nanoparticle according to claim 16.

76. (New) A use as claimed in claim 32 wherein said nanoparticle is a nanoparticle according to claim 23.

77. (New) A use as claimed in claim 32 wherein said nanoparticle is a nanoparticle according to claim 29.

78. (New) A process as claimed in claim 46 wherein the resulting nanoparticles are characterised by the features of a nanoparticle according to claim 6.

79. (New) A process as claimed in claim 46 wherein the resulting nanoparticles are characterised by the features of a nanoparticle according to claim 7.

80. (New) A process as claimed in claim 46 wherein the resulting nanoparticles are characterised by the features of a nanoparticle according to claim 15.

81. (New) A process as claimed in claim 46 wherein the resulting nanoparticles are characterised by the features of a nanoparticle according to claim 16.

82. (New) A process as claimed in claim 46 wherein the resulting nanoparticles are characterised by the features of a nanoparticle according to claim 23.

83. (New) A process as claimed in claim 46 wherein the resulting nanoparticles are characterised by the features of a nanoparticle according to claim 29.